INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/004047

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/05 A61P25/06 A61K31/16 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/15922 A (RESEARCH CORPORATION TECHNOLOGIES, INC) 28 February 2002 (2002-02-28) claims 1,15,20,34 page 1, line 10 - page 2, line 2 page 17, line 34 - page 18, line 7 page 27, line 19 - page 29, line 13 page 30, line 32 - page 31, line 6 page 50, line 25 - line 34 page 55, line 20 - line 26 page 56, line 24 - page 57, line 12	1-38
A	WO 02/074297 A (SCHWARZ PHARMA AG; SELVE, NORMA) 26 September 2002 (2002-09-26) cited in the application abstract	1-38

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2005	17/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Langer, O

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/004047

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/074784 A (SCHWARZ PHARMA AG; SELVE, NORMA) 26 September 2002 (2002-09-26) cited in the application abstract	1-38
A	US 5 773 475 A (KOHN ET AL) 30 June 1998 (1998-06-30) cited in the application the whole document	1-38
A	US 5 378 729 A (KOHN ET AL) 3 January 1995 (1995-01-03) cited in the application abstract	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/004047

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0215922	A	28-02-2002	AU	8676301 A	04-03-2002
			CA	2419285 A1	28-02-2002
			EP	1365787 A2	03-12-2003
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			US	2004097416 A1	20-05-2004
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			US	2002086828 A1	04-07-2002
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			AT	228358 T	15-12-2002
			BR	0208141 A	02-03-2004
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			AU	2002257681 A2	03-10-2002
			BR	0205823 A	21-10-2003
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			CN	1498103 A	19-05-2004
			CZ	20032763 A3	14-01-2004
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			HU	0303600 A2	01-03-2004
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			MX	PA03008467 A	08-12-2003
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			SK	12832003 A3	03-02-2004
			US	2003171300 A1	11-09-2003
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/004047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5378729 A		AU 2162192 A	08-01-1993
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		DE 69033931 D1	18-04-2002
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 32741P WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/004047	International filing date *(day/month/year)* 15.04.2005	Priority date *(day/month/year)* 16.04.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K38/05 A61P25/06 A61K31/16 A61K31/165		
Applicant SCHWARZ PHARMA AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.02.2006	13.09.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Langer, Oliver Telephone No. +31 70 340-1972

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/004047

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-36	as originally filed
Claims, Numbers	
1-38	as originally filed
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	33,34,37,38
	No:	Claims	1-32,35,36
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-38
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1. Reference is made to the following document:

D1: WO 02/15922 A (RESEARCH CORPORATION TECHNOLOGIES, INC) 28. February 2002 (2002-02-28)

V.2. Novelty (Article 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-32, 35 and 36 is not new in the sense of Article 33(2) PCT.

The document D1 (WO-A-02/15922)

discloses the use of compounds according to formula (Ib) for the treatment of migraine headaches (abstract).

The explicitly mentioned compounds of claims 14 and 24 of the application are also specifically claimed in document D1 (claims 15 and 34). Concerning the selection of enantiomers, the "D stereoisomer is preferred" in document D1 (page 31, line 6). See also the other passages cited in the search report.

The knowledge of CSD involvement in the development of migraine is not limiting the claims which are clearly directed to the treatment of migraine, see, e.g., page 1, paragraph 1; page 4, last paragraph to page 5, fist paragraph; page 8, lines 30 and 31; page 11, last paragraph. This applies regardless of the mechanism involved in migraine development.
The document D1 is clearly relating to the treatment of migraine and therefore relevant for novelty.

The disclosure of document D1 is novelty-destroying for the subject-matter of claims 1-32, 35 and 36.

V.3. Inventive Step (Article 33(3) PCT)

V.3.1. Claims 33, 34, 37 and 38

V.3.1.1. The claims 33 and 34 relate to the use of the compounds of the application in combination with "a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders" (claim 33).

V.3.1.2. The claims 37 and 38 relate to pharmaceutical compositions comprising a compound of the application in combination with "a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders" (claim 37).

V.3.1.3. Analysis of inventive step for the combination of pharmaceutically active compounds:
The act of combining two active compounds A and B for use in the treatment of a disease X is not considered to involve an inventive step if both A and B are already separately known to be effective in the treatment of X, unless an unexpected effect is obtained by combining A and B.

Knowing about the properties of A and B, the skilled person would expect at least some effect in the treatment of X when A and B are combined, unless indications to the contrary are available from the prior art.

Likewise, for a claim to the combination of A and B as a pharmaceutical combination, if A and B are already separately known for their use in therapy, the combination is not inventive.

Therefore, any claims to combinations of compounds for which no unexpected effect has been demonstrated in the application cannot be considered to involve an inventive step.

V.3.1.4. The claimed pharmaceutical activity of the compounds of the application (A) are known from D1. The second component (B) is defined by its applicability in the claimed therapeutic application (X).

V.3.1.5. The subject-matter of present claims 33, 34, 37 and 38 consequently lacks the

presence of an inventive step in the sense of Article 33(3) PCT in view of the disclosure of document D1.

V.3.2. Claims 1-32, 35 and 36

The claims 1-32, 35 and 36 are not novel in view of the disclosure of document D1, see section V.2.

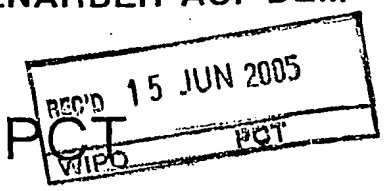
These claims consequently also lack an inventive step since they are obvious in view of the document D1 as closest prior art.

V.3.3. The subject-matter of present claims 1-38 lacks an inventive step in the sense of Article 33(3) PCT.

V.4. Industrial applicability (Article 33(4) PCT)

Present claims 1-38 relate to the provision of pharmaceutical compositions and to the second or further medical use of peptidic compounds and meet the requirements of Article 33(4) PCT.

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS



Absender: INTERNATIONALE RECHERCHENBEHÖRDE

An:

siehe Formular PCT/ISA/220

SCHRIFTLICHER BESCHEID DER INTERNATIONALEN RECHERCHENBEHÖRDE

(Regel 43*bis*.1 PCT)

	Absendedatum *(Tag/Monat/Jahr)* siehe Formular PCT/ISA/210 (Blatt 2)
Aktenzeichen des Anmelders oder Anwalts siehe Formular PCT/ISA/220	**WEITERES VORGEHEN** siehe Punkt 2 unten

Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Prioritätsdatum *(Tag/Monat/Jahr)*
PCT/EP2005/004047	15.04.2005	16.04.2004

Internationale Patentklassifikation (IPK) oder nationale Klassifikation und IPK
A61K38/05, A61P25/06, A61K31/16, A61K31/165

Anmelder
SCHWARZ PHARMA AG

1. Dieser Bescheid enthält Angaben zu folgenden Punkten:

- ☒ Feld Nr. I Grundlage des Bescheids
- ☒ Feld Nr. II Priorität
- ☐ Feld Nr. III Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
- ☐ Feld Nr. IV Mangelnde Einheitlichkeit der Erfindung
- ☒ Feld Nr. V Begründete Feststellung nach Regel 43*bis*.1(a)(i) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
- ☐ Feld Nr. VI Bestimmte angeführte Unterlagen
- ☐ Feld Nr. VII Bestimmte Mängel der internationalen Anmeldung
- ☐ Feld Nr. VIII Bestimmte Bemerkungen zur internationalen Anmeldung

2. **WEITERES VORGEHEN**

Wird ein Antrag auf internationale vorläufige Prüfung gestellt, so gilt dieser Bescheid als schriftlicher Bescheid der mit der internationalen vorläufigen Prüfung beauftragten Behörde ("IPEA"); dies trifft nicht zu, wenn der Anmelder eine andere Behörde als diese als IPEA wählt und die gewählte IPEA dem Internationale Büro nach Regel 66.1bis b) mitgeteilt hat, daß schriftliche Bescheide dieser Internationalen Recherchenbehörde nicht anerkannt werden.

Wenn dieser Bescheid wie oben vorgesehen als schriftlicher Bescheid der IPEA gilt, so wird der Anmelder aufgefordert, bei der IPEA vor Ablauf von 3 Monaten ab dem Tag, an dem das Formblatt PCT/ISA/220 abgesandt wurde oder vor Ablauf von 22 Monaten ab dem Prioritätsdatum, je nachdem, welche Frist später abläuft, eine schriftliche Stellungnahme und, wo dies angebracht ist, Änderungen einzureichen.

Weitere Optionen siehe Formblatt PCT/ISA/220.

3. Nähere Einzelheiten siehe die Anmerkungen zu Formblatt PCT/ISA/220.

Name und Postanschrift der mit der Internationalen Recherchenbehörde

Europäisches Patentamt - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Bevollmächtigter Bediensteter

Langer, O

Tel. +31 70 340-1972

SCHRIFTLICHER BESCHEID DER INTERNATIONALEN RECHERCHEBEHÖRDE

Internationales Aktenzeichen
PCT/EP2005/004047

Feld Nr. I Grundlage des Bescheids

1. Hinsichtlich der **Sprache** ist der Bescheid auf der Grundlage der internationalen Anmeldung in der Sprache erstellt worden, in der sie eingereicht wurde, sofern unter diesem Punkt nichts anderes angegeben ist.

   ☐ Der Bescheid ist auf der Grundlage einer Übersetzung aus der Originalsprache in die folgende Sprache erstellt worden, bei der es sich um die Sprache der Übersetzung handelt, die für die Zwecke der internationalen Recherche eingereicht worden ist (gemäß Regeln 12.3 und 23.1 b)).

2. Hinsichtlich der **Nucleotid- und/oder Aminosäuresequenz**, die in der internationalen Anmeldung offenbart wurde und für die beanspruchte Erfindung erforderlich ist, ist der Bescheid auf folgender Grundlage erstellt worden:

   a. Art des Materials

   ☐ Sequenzprotokoll

   ☐ Tabelle(n) zum Sequenzprotokoll

   b. Form des Materials

   ☐ in schriftlicher Form

   ☐ in computerlesbarer Form

   c. Zeitpunkt der Einreichung

   ☐ in der eingereichten internationalen Anmeldung enthalten

   ☐ zusammen mit der internationalen Anmeldung in computerlesbarer Form eingereicht

   ☐ bei der Behörde nachträglich für die Zwecke der Recherche eingereicht

3. ☐ Wurden mehr als eine Version oder Kopie eines Sequenzprotokolls und/oder einer dazugehörigen Tabelle eingereicht, so sind zusätzlich die erforderlichen Erklärungen, daß die Information in den nachgereichten oder zusätzlichen Kopien mit der Information in der Anmeldung in der eingereichten Fassung übereinstimmt bzw. nicht über sie hinausgeht, vorgelegt worden.

4. Zusätzliche Bemerkungen:

Feld Nr. II Priorität

1. ☒ Die Gültigkeit des Prioritätsanspruchs wurde nicht in Betracht gezogen, da die Internationale Recherchenbehörde über keine Abschrift der früheren Anmeldung oder, falls benötigt, Übersetzung der früheren Anmeldung verfügt. Dieser Bescheid wurde trotzdem unter der Annahme erstellt, dass der massgebliche Zeitpunkt (Regeln 43*bis*.1 und 64.1) das beanspruchte Prioritätsdatum ist.

2. ☐ Dieser Bescheid ist ohne Berücksichtigung der beanspruchten Priorität erstellt worden, da sich der Prioritätsanspruch als ungültig erwiesen hat (Regeln 43*bis*.1 und 64.1). Für die Zwecke dieses Bescheids gilt daher das vorstehend genannte internationale Anmeldedatum als das maßgebliche Datum.

3. Etwaige zusätzliche Bemerkungen:

Feld Nr. V Begründete Feststellung nach Regel 43*bis*.1(a)(i) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1. Feststellung

Neuheit	Ja:	Ansprüche 33,34,37,38
	Nein:	Ansprüche 1-32,35,36
Erfinderische Tätigkeit	Ja:	Ansprüche
	Nein:	Ansprüche 1-38
Gewerbliche Anwendbarkeit	Ja:	Ansprüche: 1-38
	Nein:	Ansprüche:

2. Unterlagen und Erklärungen:

siehe Beiblatt

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1. Reference is made to the following document:

D1: WO 02/15922 A (RESEARCH CORPORATION TECHNOLOGIES, INC) 28. February 2002 (2002-02-28)

V.2. Novelty (Article 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-32, 35 and 36 is not new in the sense of Article 33(2) PCT.

The document D1 (WO-A-02/15922)
discloses the use of compounds according to formula (Ib) for the treatment of migraine headaches (abstract).

The explicitly mentioned compounds of claims 14 and 24 of the application are also specifically claimed in document D1 (claims 15 and 34). Concerning the selection of enantiomers, the "D stereoisomer is preferred" in document D1 (page 31, line 6). See also the other passages cited in the search report.

The disclosure of document D1 is novelty-destroying for the subject-matter of claims 1-32, 35 and 36.

V.3. Inventive Step (Article 33(3) PCT)

V.3.1. Claims 33, 34, 37 and 38

V.3.1.1. The claims 33 and 34 relate to the use of the compounds of the application in combination with "a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders" (claim 33).

V.3.1.2. The claims 37 and 38 relate to pharmaceutical compositions comprising a compound of the application in combination with "a further active agent for the prevention, alleviation or/and treatment of headache or/and CSD-associated disorders" (claim 37).

V.3.1.3. Analysis of inventive step for the combination of pharmaceutically active compounds:
The act of combining two active compounds A and B for use in the treatment of a disease X is not considered to involve an inventive step if both A and B are already separately known to be effective in the treatment of X, unless an unexpected effect is obtained by combining A and B.

Knowing about the properties of A and B, the skilled person would expect at least some effect in the treatment of X when A and B are combined, unless indications to the contrary are available from the prior art.

Likewise, for a claim to the combination of A and B as a pharmaceutical combination, if A and B are already separately known for their use in therapy, the combination is not inventive.

Therefore, any claims to combinations of compounds for which no unexpected effect has been demonstrated in the application cannot be considered to involve an inventive step.

V.3.1.4. The claimed pharmaceutical activity of the compounds of the application (A) are known from D1. The second component (B) is defined by its applicability in the claimed therapeutic application (X).

V.3.1.5. The subject-matter of present claims 33, 34, 37 and 38 consequently lacks the presence of an inventive step in the sense of Article 33(3) PCT in view of the disclosure of document D1.

V.3.2. Claims 1-32, 35 and 36
The claims 1-32, 35 and 36 are not novel in view of the disclosure of document D1, see section V.2.

These claims consequently also lack an inventive step since they are obvious in view of the document D1 as closest prior art.

V.3.3. The subject-matter of present claims 1-38 lacks an inventive step in the sense of Article 33(3) PCT.

V.4. Industrial applicability (Article 33(4) PCT)

Present claims 1-38 relate to the provision of pharmaceutical compositions and to the second or further medical use of peptidic compounds and meet the requirements of Article 33(4) PCT.